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The Newer Penicillins

HAROLD J. SIMON, *M.D., Ph.D.*, Palo Alto

• **The newer penicillins give high promise of overcoming some of the few disadvantages of penicillin-G.**

They fall into three groups: The alpha-phenoxy-penicillins; the penicillinase resistant penicillins; and the penicillins with enhanced activity against gram-negative bacteria.

The newer alpha-phenoxy-penicillins offer little over alpha-phenoxy methyl penicillin (penicillin-V). As the length of the side chain is increased, absorption and attainable serum concentration is also increased, but these are questionable benefits and probably not significant for therapeusis.

The penicillinase-resistant penicillins have once more brought almost all severe staphylococcal infections within therapeutic range. One of them, methicillin, must be administered parenterally. It is the agent of choice for the treatment of severe, penicillin-G resistant staphylococcal infections, and this is its only clinical indication. Another, oxacillin, which may be administered orally, is partially resistant to gastric acid degradation, but must be given on an empty stomach. It is most useful as prolonged therapy following methicillin, in the treatment of mixed hemolytic streptococcal-penicillin-G resistant staphylococcal infections, and as primary therapy for moderately severe penicillin-G resistant staphylococcal infections.

The third group is still mostly in the experimental stage, but some strains of Proteus, E. coli, Salmonella and Shigella are highly vulnerable to their action.

Toxic and allergic reactions to the newer penicillins, and crossed allergic reactions with penicillin-G, present unsolved problems.

PENICILLIN is a most interesting compound. It was the first of the truly effective antimicrobial compounds to be discovered and widely used. It is clearly the most effective agent available against susceptible bacteria. It is almost completely nontoxic. Consequently, there is a great deal of enthusiasm today because of the promise that newer penicillins may be at hand to overcome some of the deficiencies of the parent compound.

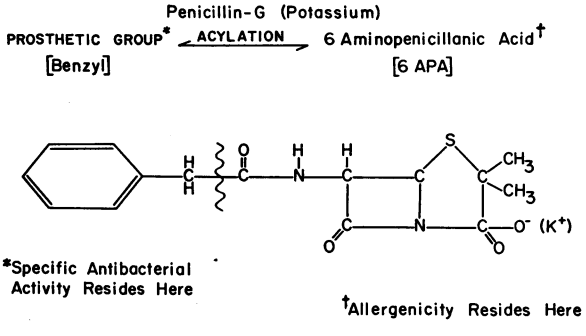

Chart 1.—Structural analysis of penicillin-G potassium.

From the Department of Medicine, Division of Infectious Diseases, Stanford University School of Medicine, Palo Alto.

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The methicillin (as Staphcillin®), oxacillin (as Prostaphlin®), and P-50 used in these studies was supplied through the courtesy of Drs. John Doyle and Eugene Morigi, Bristol Laboratories, Syracuse, New York.

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Before exploring some of the more important aspects of the newer penicillins, however, a guiding principle for antimicrobial therapy deserves to be stated clearly. No antimicrobial agent so far discovered or devised can compare with penicillin-G for effectiveness, economy, and safety. Moreover, many physicians using penicillin-G still find it difficult to apply generally available information on dosage, preparation, and route of administration to common clinical problems. It is therefore mandatory that the following remarks be interpreted in view of three basic principles:

First: The etiological agent in any disease process should be identified at all costs and its susceptibility to penicillin-G ascertained, preferably before therapy is begun, unless an urgent situation demands immediate action. The emphasis is on the word *urgent*. Such situations are rare in practice.

Second: Penicillin-G should be used whenever possible, and this usage should follow the principles developed over the past 20 years of experience with this agent.

Third: The newer penicillins should be approached with caution on several counts. Experience with these agents is limited, and the historical perspective for rational evaluation of the new agents is not yet available. Also, it is already established that the newer penicillins differ pharmacologically from penicillin-G. Absorption, distribution, and excretion data are still incomplete. However, some of these agents are excreted through the biliary system in significant amounts. With differences in their pharmacologic structure may come differences in toxicity. In addition, there are definite and significant differences in antibacterial activity between the various penicillins. Some of the newer penicillins were specifically devised to take advantage of such differences. Nevertheless, it has already been conclusively demonstrated that none of the newer homologues matches penicillin-G for anti-streptococcal or anti-pneumococcal activity. The use of the newer penicillins in such infections, already open to question on the basis of lesser activity than penicillin-G, must be carefully weighed. Differences in efficiency must be taken into account for calculation of dosages, time-schedules and routes of administration. Finally, sight must not be lost of the fact that the newer penicillins are more costly than penicillin-G by several orders of magnitude.

Nevertheless, even penicillin is still far from being the perfect antibacterial agent. Patients tend to develop allergic sensitivity to penicillin, and some of the reactions are extremely serious. Moreover, bacteria seem to learn chemistry fairly easily. Several bacterial species can produce enzymes, penicillinase and penicillin acylase, which destroy penicillin-G and some of its homologues. In addition, its activity against Gram-negative bacilli leaves much to be desired. Consequently, there are really four spheres in which research on the structure of penicillin homologues could offer significant contributions:

The development of a penicillinase-resistant penicillin molecule presented the most urgent problem. This seems now to have been solved. Methicillin (Staphcillin®), oxacillin (Prostaphlin®) and other semisynthetic penicillins have been developed by several pharmaceutical houses and are now available or are in the last phases of clinical trial.

Penicillins are needed to which patients do not manifest allergic sensitivity or allergic cross-sensitivity to other homologues. The prospect for a break-through in this direction seems very remote. The allergenic potential of the penicillins seems to reside in a very small fraction of the basic 6-aminopenicillanic acid (6-APA) molecule. This fraction seems to act as a hapten with serum or tissue protein to become a complete antigen. Penicillin residues without 6-APA are no longer active against bacteria. Penicillinase destroys the antibacterial activity but leaves the allergenic fraction intact. Penicillinase therefore has no place in clinical therapy. Probably every penicillin homologue will carry the risk of hypersensitization with it.

The problem of allergic cross-sensitivity between the penicillins is still under discussion. Most investigators believe allergic cross-sensitivity to be complete. The difficulty of eliciting clear histories of penicillin reactions in the absence of complicating factors, and the probable loss of reactivity over prolonged periods of time, make any attempt at sharp definition of allergic cross-sensitivity extremely difficult. A high proportion of patients claim penicillin allergy. Yet penicillin is present in milk, in vaccines and in the environment. Consequently, the true incidence of enduring penicillin allergy must be considerably smaller than is generally claimed, although transient hypersensitivity may occur frequently. Allergic reactions to the newer penicillins have already occurred and appear identical with those attributed to penicillin-G. A few instances of reactions to the newer penicillins have also been reported in patients whose past history of allergic sensitivity to penicillin seemed well defined. On the other hand, some patients with a history of reaction to penicillin-G have tolerated the newer penicillins. The problem of allergic cross-sensitivity is therefore not yet solved, and the prospects for solution seem remote.

The third problem concerns the administration of these agents. The oral route is always safer and usually more convenient than the parenteral route.

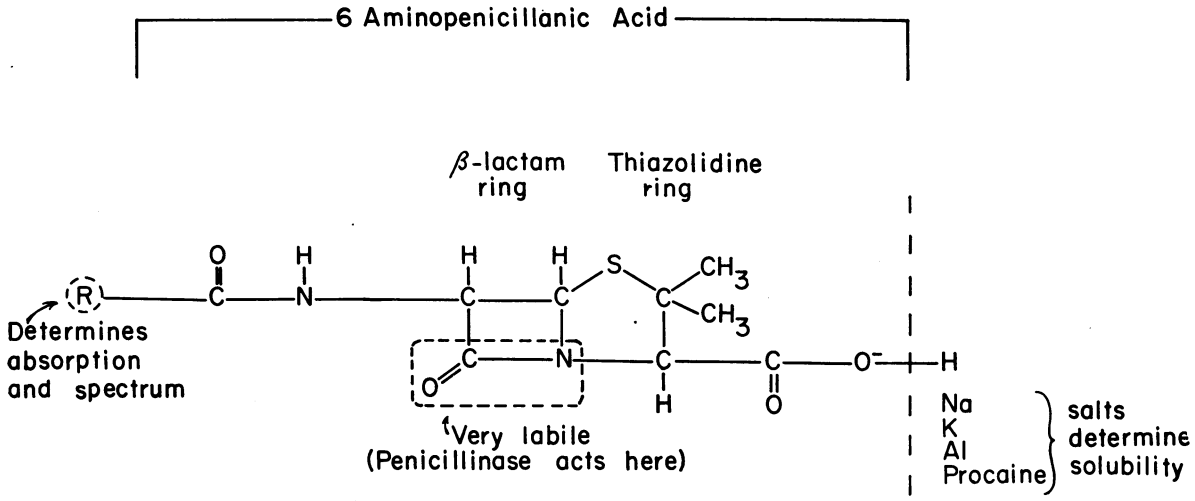
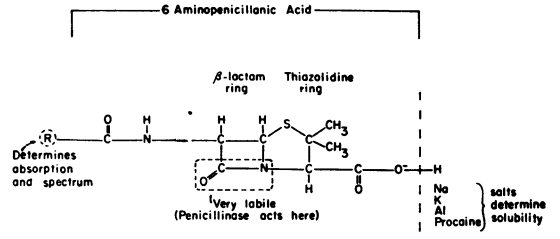


Chart 2.—Chemical formula of 6-amino-penicillanic acid and its relation to various side chains.

Consequently, penicillins are needed which overcome some of the defects of penicillin-G, can be administered by mouth at convenient intervals, and are quantitatively absorbed. The prospects are fairly bright. The whole group of phenoxy-penicillins—methyl, ethyl, and propyl—can be administered orally. They resist gastric digestion fairly well and are readily absorbed. The phenoxy-penicillins are destroyed by penicillinase. Oxacillin resists penicillinase-degradation and is absorbed following oral administration.

A fourth problem concerns the rather limited spectrum of the penicillins. Many physicians think of penicillin-G as being highly and exclusively effective against the Gram-positive cocci—pneumococcus, streptococcus, meningococcus, and some staphylococci. Penicillin-G, however, does possess significant activity against a variety of Gram-negative bacilli, although much higher doses must be employed to attain significant clinical effects. It seems desirable, therefore, to find a penicillin with decidedly enhanced anti-gram-negative bacillary activity. Several penicillin homologues with this characteristic have been synthesized and are now undergoing clinical trials. To date, however, they are still quite feeble. They are also susceptible to penicillinase. Moreover, severe diarrhea and monilial superinfection have already occurred. These are very similar to those occurring after tetracycline therapy. The broad-spectrum penicillins therefore seem to possess the antibacterial spectrum of the tetracyclines, only they are bactericidal where tetracyclines are bacteriostatic. These penicillins seem also to combine the advantages and hazards of penicillin therapy with the advantages and hazards of tetracycline therapy. In short, these broad-spectrum penicillins still leave a great deal of room for improvement.



Name(s)	Prosthetic Group®	Chemical Designation
G	[6APA]	Benzyl-penicillin
V	[6APA]	α-Phenoxymethyl-penicillin
Phenethicillin Maxipen® Syncillin® Chemipen®	[6APA]	α-Phenoxyethyl-penicillin
Brocillin® (Broxil®)	[6APA]	α-Phenoxypropyl-penicillin

Chart 3.—The chemical formulae of the prosthetic groups of the phenoxy-penicillins.

In order to understand something of the background and possible future of the newer penicillins, it seems desirable to digress for a moment into chemistry. The penicillin molecule was found to consist of three functional elements: The basic nucleus common to all penicillins is called 6-aminopenicillanic acid, or 6-APA. One part of this segment is a beta-lactam ring, the site of penicillinase action. By itself, 6-APA has no antibacterial activity. Nevertheless, the side chains which determine antibacterial activity and absorption are devoid of antibacterial activity unless coupled to 6-APA. It is

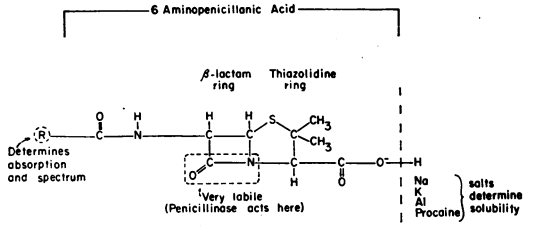
these side chains that are being substituted to make the newer penicillins. The third component is one of several cations which chiefly determines solubility.

The three phenoxy-penicillins—methyl, ethyl, and propyl—offer several advantages over penicillin-G. They are readily absorbed when taken by mouth. They are at least partially resistant to gastric acid degradation. Serum concentrations following oral administration may briefly approximate concentrations achieved following the parenteral administration of penicillin-G. It is not clear whether this is reflected in tissue concentrations, however. The three phenoxy-penicillins differ from one another in the fact that, following the same dose, peak serum concentrations are achieved earlier and range higher as the length of the side chain is increased from methyl through ethyl to propyl. Unfortunately, excretion is also more rapid in direct relationship to the length of the side chain. Consequently, high serum concentrations are maintained for a shorter time between doses. The importance of this "time under the curve" in serum is not clear. It is not known whether sustained antibacterial serum concentrations are required for the control of infections, or whether intermittent peak concentrations are desirable. The chances are that both may be important in diverse clinical conditions. Since tissue concentrations persist longer and fluctuate less, the emphasis on serum concentrations is probably misplaced anyway. Moreover, it is very likely that tissue concentrations are more important than serum concentrations. These pharmacological data should be remembered when the phenoxy-penicillins are employed.

The antibacterial spectrum of the phenoxy-penicillins does not differ significantly from that of penicillin-G, although most susceptible strains require greater concentrations of the phenoxy-penicillins for inhibition. The differences are slight, and the dosages usually recommended make up for these disparities.

The disadvantages of the phenoxy-penicillins lie in their cost, which is much greater than for penicillin-G, and in their susceptibility to penicillinase. They are somewhat more resistant to this enzyme than is penicillin-G, but the differences are probably of no clinical significance. Patients with allergic sensitivity to penicillin-G should be presumed sensitive to these newer agents also. To date, there have been no new toxic reactions reported for this group of compounds.

The most exciting aspect of the phenoxy-penicillins is not their antibacterial activity; it is the fact that these agents represent an almost immediate application of basic chemical research to clinical medicine. Less than three years have elapsed since



SOME IMPORTANT PENICILLINS

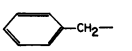
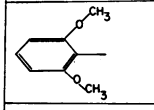
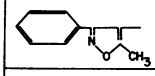
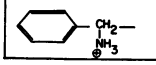
Prosthetic Group®	Name(s)	Route of Administration	Penicillinase	Spectrum
	Benzyl-penicillin Penicillin G	Oral, intramuscular, intravenous	susceptible	Gram positive cocci High doses for some Proteus, Salmonella
	Methicillin Staphcillin®	Intramuscular, intravenous	resistant	Penicillin-resistant staphylococci
	P-12 Prostaphlin® Oxacillin	Oral, intramuscular	resistant	Penicillin-resistant staphylococci other gram positive cocci
	P-50 Penbritin®	Oral, intramuscular	susceptible	E. coli, Salmonella, Shigella, some Proteus, Gram positive cocci

Chart 4.—Structural and functional analysis of the penicillin molecule and some of its more important homologues. (Modified from Dowling, H. F., C. Clin. Pharm. Therap., 1961, 2:573, with kind permission of C. V. Mosby Co.)

the isolation of 6-APA. These newer penicillins already have been available for over two years. Even at the time of this writing, a new compound, alpha-phenoxy-benzyl penicillin (Penspec®), is making its appearance in England. It seems to promise still greater achievements in the phenoxy-penicillin range, but experience is severely limited. The synthesis of these compounds opened an entirely new field, and the next substance truly represents a breakthrough for clinical medicine.

Methicillin, 2,6 dimethoxyphenyl-penicillin, (Staphcillin®), was the first of the new penicillins to possess essentially complete resistance to penicillinase. Essentially all clinically important instances of penicillin-resistant staphylococcal infections are due to penicillinase elaboration on the part of the infecting micro-organisms. Consequently, physicians confronted with penicillin-resistant staphylococcal infections have been given a new and potent weapon. Enthusiasm was limited initially by an apprehension that the experimental results might not be fulfilled in actual practice. These doubts are now dispelled.

Methicillin is highly effective against all but approximately 1 per cent of penicillin-resistant staphylococci. Almost overnight, multiple antimicrobial regimens have become obsolete. Vancomycin, the agent upon which we had to rely previously for bactericidal anti-staphylococcal activity in penicillin-

resistant infections, is now relegated to a minor supporting role. Methicillin is the agent of choice for all serious staphylococcal infections unless allergic sensitivity precludes its use. Experience to date already indicates that methicillin, properly used, once again restores the effectiveness of anti-staphylococcal therapy to the high level experienced when penicillin-G first became available. It must be remembered that mortality from staphylococcal infections in the middle and latter 1950's was not significantly less than it had been before the introduction of penicillin-G. The key, however, lies in the phrase *properly used.*

Methicillin must be administered parenterally. The preferred route is by means of intermittent intramuscular or intravenous injections. One gram every three to four hours is the recommended adult dose. Intravenous injections may be made directly into the vein, or into the tubing of a continuous infusion of saline or dextrose in water. On certain occasions, however, it may become necessary to use a continuous infusion of methicillin. This requires precautionary measures.

Solutions of methicillin are quite unstable. Initially, dosages of 6 to 8 grams of methicillin given intramuscularly or intravenously in divided doses or by continuous infusion, seemed to be satisfactory on the basis of experimental and clinical data until several treatment failures occurred. Even now, some physicians order dosages of 12 to 20 grams daily. Since severe staphylococcal infections usually require several weeks of sustained therapy, and the drug is very expensive, this development seemed to threaten the widespread use of methicillin. At least some of this confusion is due to inactivation of methicillin in the infusion bottle.

It is not generally appreciated that the pH of normal saline solution is usually close to 6.0, and the pH of 5 per cent dextrose in water may range to 4.5, depending on the amount of gluconic acid formed during sterilization or on the shelf after exposure to light or heat. Methicillin is highly unstable at acid pH and is readily inactivated unless infusions are buffered. I generally use sodium bicarbonate in amounts sufficient to turn pH test paper strips to pH 7.2 to 7.4. Generally, 20 to 25 ml. (18 to 23 mEq.) per liter of infusion suffice for this purpose. This seems cumbersome. Nevertheless, it seems the only way to administer this agent by means of continuous infusion without excessive inactivation. Additionally, the solutions should not be made up until immediately before use. Even though alkalinization is carried out, the infusion should be changed at least every eight hours. Unless these directions are followed, higher dosages are necessary, with greater expense to the patient.

TABLE 1.—*Administration of Methicillin*

INTRAMUSCULARLY: 1 gram every three or four hours.
INTRAVENOUSLY: 1 gram every three to four hours directly into the vein or into the tubing of a continuous infusion.
INTRAVENOUSLY:* At least 6 to 8 grams per day by continuous infusion.
INDICATIONS: Only for penicillin-G resistant staphylococcal infections in patients not known to have allergic sensitivity to penicillin-G.
*CAUTION: Alkalinize infusions to pH 7.2 to 7.4. Change infusions every eight hours. Do not add other drugs to infusion.

Intramuscular administration is generally safe and reasonably well tolerated. However, patients with bleeding tendencies do not tolerate the intramuscular route well. Patients with diabetes mellitus, patients in shock and those with other circulatory disorders may not absorb the drug from intramuscular depots. Intravenous administration then becomes the method of choice.

One other note of caution is indicated. The lability and chemical reactivity of methicillin make it unwise to use vitamins or other drugs in the same infusion.

Methicillin has three disadvantages: It must be given parenterally; it is either completely degraded or not absorbed from the intestinal tract; it possesses only feeble activity against bacteria other than penicillin-resistant staphylococci. Moreover, allergic sensitivity to penicillin probably means sensitivity to methicillin also. Consequently, the only indication for methicillin seems to be penicillin-G resistant staphylococcal infections occurring in patients not allergic to penicillin. Methicillin is expensive and unstable. Therefore, while an extremely useful addition to the anti-staphylococcal armamentarium, it still leaves much to be desired.

Methicillin is primarily cleared through the kidneys. Very little appears in the bile. Evidence of renal impairment has already been reported in a few patients to whom methicillin was being administered. One case of bone marrow depression has recently been reported, and I have seen another in which this condition was attributed to methicillin. There may be other as yet undiscovered toxic hazards. As with all new drugs, continuous vigilance is the only safeguard we can offer our patients.

More recently, a group of semisynthetic penicillins has appeared whose chief virtue overcomes one of the serious defects of methicillin. This group, of which oxacillin (Prostaphlin®) is the prototype, combines penicillinase-resistance with adequacy of absorption following oral administration. Milligram for milligram, these agents are more effective than methicillin. This greater activity extends across the penicillin-G-resistant staphylococci to the other Gram-positive cocci but still does not equal the

activity of penicillin-G against these micro-organisms. Experience with this newer penicillin has been almost completely limited to use of the drug by mouth, although parenteral forms are being tested. It has already become clear that severe staphylococcal infections can be treated with oxacillin therapy alone, although this is not yet recommended. The intelligent use of these agents also requires some understanding of their pharmacological properties.

Oxacillin is subject to degradation by gastric acid and must be administered on an empty stomach. In addition, serum concentrations are not well maintained. Dosages should therefore not be spaced more than four hours apart—at least for serious infections and until more data become available on tissue concentrations. In general, we recommend doses of 100 mg. by mouth per kilogram per day in divided doses at four-hour intervals spaced around meals. Administration should take place no less than one hour before nor sooner than two hours after meals. (If daytime meals fall at 8 a.m., 12 noon, and 7 p.m., the dose sequence runs something like this: 7 a.m., 11 a.m., 3 p.m., 6 p.m., 10 p.m., 2 a.m.) Effective serum concentrations are maintained for slightly more than two of the four hours. If administration coincides with a meal, however, essentially no activity is detectable in the serum.

The precise role of the oxacillin group of penicillins is still difficult to assess. Experience is still too limited and the use of these antibiotics as first line agents in the treatment of severe staphylococcal infections—while probably appropriate—cannot yet be recommended. Three spheres of usefulness can now be defined, however:

1. Their main use lies in the prolonged treatment of severe, penicillin-resistant staphylococcal infections after parenteral methicillin therapy has allowed some stabilization of the clinical situation.

2. Moderately severe infections—osteomyelitis, progressive cellulitis and pyelonephritis, for example—can be treated with oral administration of oxacillin alone, always provided that careful follow-up cultures and clinical observation are carried out and care is taken not to interfere with absorption.

3. These agents are also most useful for the treatment of mixed hemolytic streptococcal-staphylococcal infections when the staphylococcal component is penicillin-G-resistant. Examples include atopic eczema, impetigo and streptococcal pharyngitis. Despite the clearly penicillin-G-susceptible nature of Group A hemolytic streptococci, penicillin-G may fail when penicillinase-producing staphylococci share the infected sites. Such failures are presumed due to local inactivation of penicillin-G by the penicillinase that is produced. The small amounts of penicillin usually used in such infections are inadequate to overcome this form of biological antagonism. Oxacillin and its congeners are definitely indicated in such situations and have proven highly satisfactory.

TABLE 2.—*Administration of Oxacillin*

ORALLY: 100 mg. per kilogram of body weight per day divided into four-hourly doses and spaced around meals.*

INTRAMUSCULARLY: 50 mg. per kilogram of body weight per day divided into four-hourly doses.†

*CAUTION: For oral use, administer on an empty stomach. Oral therapy administered no less than one hour before meals nor sooner than two hours after meals.

†Oxacillin not yet available for parenteral administration.

Unfortunately, allergic reactions have already been observed, and allergic cross-sensitivity can be expected in patients who are sensitive to penicillin-G. Diarrhea, epigastric pain, nausea, and bitter taste occur commonly at the doses recommended. Some instances of increases in serum glutamic oxaloacetic transaminase (SGOT) activity have been reported. The elevated SGOT reverted to normal when the drug was discontinued. These drugs are also much more expensive than penicillin-G. Nevertheless, they promise to be very useful.

Other developments in the penicillin series seem potentially to have even greater promise for the future. Penicillin-G has been known for its activity against some strains of Proteus, E. coli, and Salmonella. Most of these anti-gram-negative bacillary activities are more striking in the test tube than on clinical application. Very recently a new penicillin has been synthesized in which the anti-gram-negative bacillary activity of penicillin-G has been enhanced. The importance of this development cannot be overemphasized in view of the progressive increase and severity of such infections occurring in hospitals.

The prototype of this group is alpha-aminobenzylpenicillin, (Penbritin®), or P-50. P-50 retains most of the anti-gram-positive coccal activity of penicillin-G. In addition, however, it is significantly more effective than penicillin-G against many strains of Proteus, most strains of Salmonella and Shigella, E. coli and Klebsiella-Aerobacter. P-50 is useless against other strains of Proteus and Pseudomonas. It is destroyed by penicillinase. P-50 therefore combines the bactericidal properties of penicillin-G with the broad spectrum coverage of tetracycline. Unfortunately, P-50 does not come as an unmixed blessing.

Clinical experiences are still meager. Nevertheless, typical penicillin rashes are already attributed to P-50. Their incidence cannot be evaluated thus far, but seem no less than with penicillin-G. Fulminant diarrhea and moniliasis have also been encountered. Consequently, while P-50 seems to combine the beneficial attributes of penicillin-G and tetracycline,

it also adds their major side effects. Moreover, swelling of the mouth and lips has been seen in experimental animals, but not yet in human beings. This completely new reaction once again emphasizes the potentiality for new reactions inherent in all new drugs no matter what their genealogy.

Dosage schedules are not fully established. This agent is still in short supply and will undoubtedly be very expensive. Nonetheless, it is the first of what promises to be a most interesting and useful series of penicillins. Their chief virtues will lie in their anti-gram-negative bacillary activity. Several other preparations are now undergoing clinical trials, but none is as close to P-50 with respect to clinical applicability.

Pharmacologically, the newer penicillins differ from penicillin-G in at least one major category. They are all more or less excreted in the bile. Renal excretion is less prominent, and new pharmacological possibilities are presented.

Biliary excretion of active drug might lead to internal recirculation and cumulation. Hepatic dysfunction, never of consequence with penicillin-G, might seriously affect the clearance of the newer compounds. The need for hepatic participation in their metabolism sets the stage for potential hepatic and other toxicities. These considerations must be weighed when the new penicillins are used.

The smaller fraction of renal excretion also influences one other aspect of penicillin therapy. Probenecid (Benemid®) blocks the renal clearance of penicillin-G. The addition of probenecid to penicillin-G therapy increases both the peak concentrations attained and the duration of penicillin-G persistence in body fluids. Interestingly, probenecid also increases and prolongs significantly the serum concentrations of the newer penicillins. This property might be used to make smaller doses stretch further. In general, however, the use of probenecid cannot be recommended. It is a sulfonamide derivative and hypersensitivity reactions are not uncommon. Added to those associated with penicillin, these reactions would raise the risk of side effects to high orders of probability. Besides, as was previously noted, the significance of high or sustained serum concentrations is still unknown.

The vital question of bacterial resistance to the penicillinase-resistant penicillins cannot yet be answered fully. Very few methicillin-resistant coagulase positive staphylococci have been recovered from treated patients. Coagulase-negative staphylococci, on the other hand, have developed very high orders of resistance *in vitro* and *in vivo*. Coagulase-positive staphylococci have been rendered partially resistant to methicillin *in vitro*, but seem to lose some of their virulence in the process. Unfortunately, resistance to methicillin seems to cross with resistance to the other penicillinase-resistant agents. The resistant strains do not destroy the newer penicillins, but seem instead to become drug-indifferent. On the basis of this evidence, therefore, methicillin and allied resistance problems may once again rise to plague physicians.

Since methicillin is used almost exclusively in hospitals, it was anticipated that the appearance of resistant strains would occur first and be chiefly limited to hospital settings. Restriction of this drug was therefore rational. The development of oxacillin and its congeners and the cross-resistance problem between these and methicillin casts a new light on the problem. It is likely that many ambulant patients will be treated inadequately. Resistant strains may therefore appear and accumulate in the community as well as in the hospital. This would duplicate past experiences with other antimicrobial agents. Consequently, it becomes vitally important to use these potent, valuable agents only on specific indication, in effective doses and for long enough periods in order to minimize the emergence of resistant bacterial strains.

300 Pasteur Drive, Palo Alto.